REMARKS

Reconsideration is respectfully requested. Claims 1, 12, and 22 have been amended. New claims 33-41 have been added. Claims 1-41 will be pending after entry of these amendments.

Claims 1, 12, and 22 have been amended to indicate that the encoded polypeptide is "a cytochrome P450 which converts an active brassinosteroid to an inactive brassinosteroid." Support for this limitation may be found throughout the specification as filed. For example, in the Summary on page 5, lines 21-27, the specification indicates that "the *bas1* gene encodes a cytochrome P450 (CYP72B1) which has a role in brassinosteroid signaling or synthesis." The Summary further indicates that "[b]iochemical analysis indicates that CYP72B1 is a C-26 hydroxylase of brassinolide targeting it for inactivation."

New claims 33-41 have been added with this amendment. Support for the percent identity in claims 33, 34, 36, 37, 39 and 40 is found on page 13, lines 21-24 of the specification. Support for the hybridization wash conditions in claims 35, 38, and 41 is found on page 17, lines 5-13 of the specification.

Elections/Restrictions

Applicants acknowledge that the restriction requirement has been made final.

Information Disclosure Statement

Applicants thank the Examiner for considering the references submitted with the Information Disclosure Statement and returning the signed Form 1449. Applicants submit a Supplemental Information Disclosure Statement (SIDS) with the present response. Applicants respectfully request that the Examiner review and consider these references as well.

Telephonic Interview

Applicants thank Examiner Collins for the very helpful telephonic interview conducted on September 21, 2004. The state of the art as of filing of the priority application as it relates to the written description rejection and the enablement rejection was discussed at length. This response is submitted pursuant to that discussion.

Claim Objections

The Examiner has objected to claim 12 for reciting a sequence directed to a non-elected invention. Claim 12 has been amended by deleting the non-elected invention. In light of this, Applicants request that the Examiner withdraw the objection.

Claim Rejections – 35 USC § 112, first paragraph, Written Description

The Examiner has rejected claims 1-4, 7-13, 15, 17-23, 25, and 27-32 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner has asserted that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner explains her rejection by noting that the Federal Circuit has recently stated "A description of a genus of cDNAs may be achieved by means of recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." The Examiner further indicates "[i]n the instant case Applicant has not described a representative number of species falling within the scope of the claimed genus of sequences comprising at least one structural gene encoding a BAS1 polypeptide, nor the structural features unique to the genus."

The rejection is avoided by the amendments to the claims. Applicants have amended claims 1 and 12 (and those dependent thereon) to recite that the "BAS1 polypeptide is a cytochrome P450 which converts an active brassinosteroid to an inactive brassinosteroid." The amendment of the claims to include the substrate for the BAS1 polypeptide provides a key structural feature unique to the genus. The amended claims clearly convey to those of skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

As was discussed in the telephonic interview, at the time of the filing of the present application a large number of representative species falling within the scope of the claimed genus were known. In fact, more than 200 P450 sequences were known. (see Werck-Reichhart and Feyereisen, pages 3003.1, submitted in an SIDS with this response, the "Werck Review") From years of studies of P450 enzymes, there is a large body of work including several crystal structures of cytochrome P450s (see Werck Reference pages 3003.2-3003.3). The entire catalytic cycle of the

cytochrome P450s, determined from a series of crystal structures captured through the cycle, was published contemporaneous to the priority date of the application, and even then only three of the seven intermediate structures in the catalytic pathway were new (see Schlichting, *et al.* Science (2000) 287:1615-1622, submitted in the SIDS). As detailed in the review, the cytochrome P450s all have the same structural fold and all share the same enzymatic mechanism. Thus, a large number of species falling within the scope of the claimed genus of sequences comprising at least one structural gene encoding a BAS1 polypeptide (where the BAS1 polypeptide is a cytochrome P450) were known to those of skill in the art at the time the application was filed. Furthermore, because of the vast information known about cytochrome P450s including sequence alignments, mutagenic data and crystal structures relating the important residues in the sequence to the known catalytic function, the structural features unique to the genus (cytochrome P450) were known.

Applicants have, furthermore, identified a functional feature of the cytochrome P450 genus. Applicants have identified the substrate of the disclosed cytochrome P450 as active brassinosteroids and the function of the disclosed cytochrome P450 as catabolism of the active brassinosteroids, *i.e.*, inactivation of the brassinosteroids. Indeed, Applicants have identified these features despite significant difficulties in studying plant P450 enzymes as pointed out by the Examiner (Office Action, page 7, citing Mizutani et al., (Plant Molecular Biology, Vol. 37, pages 37-52, 1998, "it has been difficult to elucidate physiological functions for cloned sequences encoding plant cytochrome P450s.") The claims have been amended to require that the cytochrome P450 of the invention uses as its substrate an active brassinosteroid.

One of skill in the art can readily identify the range of cytochrome P450 sequences that will likely bind to active brassinosteroid substrate. By way of example, a recently published paper using amino acid sequences, crystal structures, and modeling programs available as of the priority date of this application demonstrates that four highly divergent plant cytochrome P450s share similar structurally based strategies for substrate binding. (see *Rupasinghe et al. Protein Engineering, (2003) 16:721-731*, submitted in the SIDS) The four enzymes bind to their substrates in a similar manner and the substrate regions involved in binding to similar regions of their respective substrates showed a high degree of conservation even though the four enzymes share only about 13% amino acid identity. Applicants have identified a sequence, i.e., BAS1, and a substrate,

i.e., active rassinosteroid. These data, together with crystal structure modeling programs will allow one to identify related BAS1 sequences useful in the practice of the invention.

Thus, one of skill in the art would understand that Applicants had possession of the invention at the time of filing the application because of (a) the large number of known cytochrome P450 sequences; (b) the readily determinable relationship between the structure and the function binding of the substrate - an active brassinosteroid; (c) the ease of producing a plant from a transformed plant cell and (d) the ease of selecting plants exhibiting a dwarf adult stature.

In light of this, Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-4, 7-13, 15, 17-23, 25, and 27-32 based upon 35 U.S.C. § 112, first paragraph, written description.

Claim Rejections – 35 USC § 112, first paragraph, Enablement

The Examiner has rejected claims 1-4, 7-13, 15, 17-23, 25, and 27-32 under 35 U.S.C. 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants respectfully disagree. The specification provides more that adequate support to enable one of skill in the art to make and use the claimed invention commensurate in scope with the claimed invention. The Examiner has asserted that undue experimentation would be required. However, as indicated in *In re Wands*, undue experimentation is evaluated based upon eight factors, including the quantity of experimentation, the amount of direction or guidance provided, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In the present application, undue experimentation is not required for one of skill in the art to make and use the invention commensurate in scope with the claims. Application of the *Wands* factors to the claimed invention clearly supports this.

The first *Wands* factor is the quantity of experimentation necessary. The quantity of experimentation is not undue. The molecular biology techniques for generating the vectors are routine and therefore not undue experimentation. The techniques for plant transformation are also routine and therefore not undue experimentation. Identification of polypeptides that are cytochrome

P450s which use active brassinosteroids as substrate is a routine matter. As discussed above with regard to the written description rejection, there is a vast wealth of knowledge available regarding cytochrome P450s. This vast knowledge reduces the experimentation needed by allowing those of skill in the art to reject sequences that will clearly not function based upon knowledge of the key residues involved in function of the cytochrome P450s, for example, enzymatic activity and substrate specificity, and upon knowledge of regions of high sequence variability that do not affect function.

Finally, screening for plants with the claimed dwarf phenotype is routine and therefore not undue experimentation. As discussed in the telephonic interview, such screening is so routine that one of the inventors, Professor Michael Neff of Washington University at Saint Louis teaches undergraduates in his laboratory class to perform such a screening as an undergraduate laboratory exercise. It is does not matter that it may take a fair amount of work to screen through multiple sequences to find those that function as claimed. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification or state of the art in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

The second *Wands* factor is the amount of direction or guidance provided. As discussed above with regard to the first *Wands* factor, the nature of the experimentation is all routine, so the techniques used need not be disclosed, and yet they are disclosed in actual working examples. Furthermore, the specification, at page 59, line 10 to page 62, line 7, discusses methods of identifying additional BAS1-encoding genes by hybridization techniques and degenerate PCR techniques, for example. Thus, there is an adequate amount of guidance provided as how to identify additional sequences.

The third *Wands* factor is the presence or absence of working examples. Applicants have taught actual working examples of the BAS1-encoding gene and plants transformed with one such gene. Examples 1-3 (page 74 through page 77, line 8) teach the isolation of a BAS1 encoding gene. Furthermore, other examples provide an abundant disclosure characterizing the functional and structural characteristics of the expression of BAS1, including effect on plant size, brassinolide dose

response, and biochemical analysis of the enzymatic activity. Thus Applicants have provided actual working examples.

The fourth *Wands* factor is the nature of the invention. Making and using the invention requires only routine molecular biology techniques and is a matter of routine testing of sequences related to those disclosed. Furthermore, in this instance, the *bas1* gene is part of a large family of enzymes that share the same mechanism and differ primarily in substrate preference.

The fifth *Wands* factor is the state of the prior art. The state of the art is high. As of the priority date of March 16, 1999, molecular biology techniques were well worked out and included a high degree of automation due to, for example, genome sequencing. In addition, as discussed above in regard to the written description rejection, the cytochrome P450 field is very well developed with a large number of identified sequences and abundant structural, biochemical and mutagenic data available to give guidance to one of skill in the art to identify additional BAS1 polypeptides that have a high likelihood of functioning. Thus, one of skill in the art will be able to make and use the invention commensurate with the scope of the claims owing to this body of knowledge available regarding cytochrome P450s.

The sixth *Wands* factor is the relative skill of those in the art. The skill in the art is high. Plant transformation is typically done by graduate level research scientists or higher. Such research scientists are well versed in the molecular biology and screening techniques required by the claimed invention.

The seventh *Wands* factor is the predictability or unpredictability of the art. Applicants respectfully submit that in view of the vast body of knowledge regarding cytochrome P450 enzymes, and the ease with which transgenic plants can be generated, the predictability of the art pertaining to the invention is high. A large number of P450 enzymes have been identified. Sequence alignment studies, along with computer models of crystal structures of the enzymes have allowed the identification of regions of the P450s that may vary with no change in function. Futhermore, the production of transgenic plants is quite predictable. As discussed above, Professor Michael Neff utilizes plant transformation techniques with his undergraduate students. The high predictability of the plant transformation techniques permits students to successfully perform experiments in a timely and reproducible manner. Applicants submit that the vast array of

availableinformation on P450 enzymes coupled with the high predictability of making transgenic plants with Bas-1 related sequences can readily and predictably be used to identify Bas-1 related sequences.The eighth *Wands* factor is the breadth of the claims. Given the disclosure of an exemplary gene sequence and the abundant functional and structural characterization of the gene and its expression, the claims are not unduly broad. In addition, the claims as currently amended require that the sequence is a cytochrome P450 which carries with it known structural, functional and sequence limits, require that the cytochrome P450 use as its substrate active brassinosteroids, and clearly define a function that may be easily screened. Therefore, the breadth of the claims is not unduly broad.

Thus, given that most if not all of the Wands factors weigh in the favor of Applicants, the invention as claimed would not require undue experimentation by one of skill in the art to make and use the invention commensurate with the scope of the invention. Applicants respectfully request that the Examiner withdraw the rejection of claims 1-4, 7-13, 15, 17-23, 25, and 27-32 based upon 35 U.S.C. § 112, first paragraph, enablement.

Claim Rejections – 35 USC § 102(b)

The Examiner has rejected claims 12-13, 15, 17-18, 21-23, 25, 27-29 and 31 under 35 U.S.C. § 102(b) as being allegedly anticipated by Mangold *et al.* (Plant Science, Vol. 96, pages 129-136, 1994). Applicants respectfully traverse the rejection.

The Examiner has asserted that the sequence used by Mangold *et al.* is necessarily a BAS1 polypeptide. Amended independent claims 12 and 22 recite that the polypeptide is a cytochrome P450 which uses an active brassinosteroid as a substrate. While Mangold *et al.* teach a cytochrome P450 enzyme in the CYP72 family that is in the same family as the *bas1* gene disclosed in the present application, the cytochrome P450 disclosed in Mangold *et al.* does not use an active brassinosteroid as a substrate. Rather, the substrate for the *Catharanthus roseus* gene, i.e., the gene disclosed in Mangold *et al.,* is loganin (Irmler *et al.* (Plant Journal (2000) 24(6), 797-804, included in the enclosed SIDS) Loganin is not an active brassinosteroid. Thus, Mangold *et al.* fail to teach a polypeptide that is a cytochrome P450 which uses an active brassinosteroid as a substrate. Therefore, Mangold *et al.* fail to anticipate the claimed invention.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 12-13, 15, 17-18, 21-23, 25, 27-29 and 31 based upon 35 U.S.C. § 102(b).

Claim Rejections – 35 USC § 103

The Examiner has rejected claims 20, 30, and 32 under 35 U.S.C.§ 103 as being allegedly unpatentable over Mangold *et al.* (Plant Science, Vol. 96, pages 129-136, 1994) in view of Persans *et al.* (Plant Physiology, 1995, Vol. 109, pages 1483-1490), and in further view of Lyznik *et al.* (The Plant Journal, 1995, Vol. 8, No. 2, pages 177-186). Applicants respectfully traverse the rejection.

Claims 20, 30 and 32 depend from amended independent claims 12 and 22 which now recite that the polypeptide is a cytochrome P450 which uses an active brassinosteroid as a substrate. As discussed above, Mangold *et al.* fail to teach a polypeptide that is a cytochrome P450 which uses an active brassinosteroid as a substrate. The deficiencies of Mangold *et al.* can not be cured by reliance on Persans *et al.* Persans et al. do not teach or suggest a cytochrome P450 that uses an active brassinosteroid as a substrate. Similarly, the deficiencies of Mangold *et al.* can not be cured by reliance on Lynik *et al.* Lynik *et al.* do not teach or suggest a cytochrome P450 that uses an active brassinosteroid as a substrate. Since neither Persans *et al.* nor Lyznik *et al.* teach or suggest a cytochrome P450 which uses an active brassinosteroid as a substrate, there is no *prima facie* case of obviousness for lack of one of the elements of the claims. Therefore, Mangold *et al*, in view of Persans *et al.*, and in further view of Lyznik *et al.* fail to render the claimed invention obvious.

Applicants respectfully request that the Examiner withdraw the rejection of claims 20, 30, and 32 based upon 35 U.S.C. § 103.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **532792000610.** However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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